Clinical trial results:
An open-label extension study to evaluate the long-term safety and tolerability of Idalopirdine (Lu AE58054) as adjunctive treatment to donepezil in patients with mild-moderate Alzheimer's disease

Summary

EudraCT number	2013-000001-23
Trial protocol	CZ DE EE IT BE LT ES DK BG PT GB HU FI HR
Global end of trial date	06 July 2017

Results information

Result version number	v1 (current)
This version publication date	21 July 2018
First version publication date	21 July 2018

Trial information

Trial identification

Sponsor protocol code	14861B STAR EXTENSION

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02079246
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 July 2017
Global end of trial reached?	Yes
Global end of trial date	06 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Open-label Treatment Period (OLEX): To evaluate the long-term safety and tolerability of idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate AD.

Open-label Treatment Period with Memantine (OLEX-MEM): To evaluate the safety and tolerability of concomitant treatment with idalopirdine, memantine and donepezil in patients with AD.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996).

Background therapy:

This is an interventional, multi-national, multi-site, open-label extension study in patients with mild to moderate AD who completed the 24-week lead-in study 14861A (NCT01955161) or 14862A (NCT02006641).

Patients received 28-weeks of open-label treatment with idalopirdine 60 mg/day (option to reduce to 30 mg/day) as adjunctive treatment to donepezil. Approximately 100 patients, who had completed the initial 28-week period (OLEX), were included in a 24 week open-label treatment period with memantine (OLEX-MEM) that evaluated the safety and tolerability of concomitant memantine therapy in patients who were already on a stable treatment with idalopirdine and donepezil and for whom memantine treatment was clinically indicated.

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 139
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	United Kingdom: 66
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Bulgaria: 52
Country: Number of subjects enrolled	Czech Republic: 135
Country: Number of subjects enrolled	Denmark: 11

Country: Number of subjects enrolled	Estonia: 44
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 71
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 82
Country: Number of subjects enrolled	Lithuania: 34
Country: Number of subjects enrolled	United States: 236
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Brazil: 30
Country: Number of subjects enrolled	Chile: 79
Country: Number of subjects enrolled	Argentina: 119
Country: Number of subjects enrolled	Ukraine: 47
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	South Africa: 39
Country: Number of subjects enrolled	Israel: 5
Worldwide total number of subjects	1462
EEA total number of subjects	801

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	215
From 65 to 84 years	1135
85 years and over	112

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study.

Period 1

Period 1 title	OLEX
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Idalopirdine 60 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Idalopirdine 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Idalopirdine 60 mg adjunct to 10 mg donepezil. The dose of idalopirdine could be decreased from 60 mg to 30 mg if 60 mg was not well tolerated. The dose of donepezil was to be maintained throughout the study.

Number of subjects in period 1	Idalopirdine 60 mg
Started	1462
Completed	1235
Not completed	227
Adverse event, serious fatal	11
Insufficient compliance	2
Withdrawal of caregiver consent	1
Worsening of condition	1
Results of the lead-in studies	58
Moved to nursing home	1
Consent withdrawn by subject	60
Adverse event, non-fatal	66
Caregiver unavailable	3
Lost to follow-up	6
Disallowed medication	8

Protocol deviation	6
Lack of efficacy	3
Coordinator decision	1

Period 2	
Period 2 title	OLEX-MEM
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Idalopirdine 60 mg + memantine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Idalopirdine 60 mg + memantine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Idalopirdine 60 mg as adjunct to 10 mg donepezil and memantine (patient's individualised maintenance dose, either immediate-release (IR) 20 mg/day (recommended target dose) or extended release (XR) 28 mg/day (recommended target dose). Memantine was administered to approximately 100 patients included in the OLEX-MEM. The dose of idalopirdine could be decreased from 60 mg to 30 mg if 60 mg was not well tolerated. The dose of donepezil was to be maintained throughout the study. The dose of memantine could be changed at any time throughout the study.

Number of subjects in period 2[1]	Idalopirdine 60 mg + memantine
Started	101
Completed	82
Not completed	19
Moved to nursing home	3
Consent withdrawn by subject	7
Adverse event, non-fatal	6
Lost to follow-up	1
Protocol deviation	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 101 patients, who had completed the initial 28-week period (OLEX), were included in a 24 week open-label treatment period with memantine (OLEX-MEM) that evaluated the safety and tolerability of concomitant memantine therapy in patients who were already on a stable treatment with idalopirdine and donepezil and for whom memantine treatment was clinically indicated.

Baseline characteristics

Reporting groups	
Reporting group title	OLEX

Reporting group description: -

Reporting group values	OLEX	Total	
Number of subjects	1462	1462	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	73.7		
standard deviation	± 8.2	-	
Gender categorical Units: Subjects			
Female	922	922	
Male	540	540	
Race Units: Subjects			
Asian	63	63	
Black or African American	17	17	
White	1318	1318	
Unknown or Not Reported	62	62	
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2	2	

End points

End points reporting groups

Reporting group title	Idalopirdine 60 mg
Reporting group description: -	
Reporting group title	Idalopirdine 60 mg + memantine
Reporting group description: -	
Subject analysis set title	Idalopirdin 60 mg (OLEX): patients from lead-in study 14861A
Subject analysis set type	Full analysis
Subject analysis set description: Idalopirdin 60 mg (OLEX): patients from lead-in study 14861	
Subject analysis set title	Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A
Subject analysis set type	Full analysis
Subject analysis set description: Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A	

Primary: Number of Treatment Emergent Adverse Events (TEAEs) in the OLEX

End point title	Number of Treatment Emergent Adverse Events (TEAEs) in the OLEX[1]
End point description: A TEAE is an adverse event that starts or increases in intensity after the date of Baseline II (start of OLEX)	
End point type	Primary
End point timeframe: Baseline II (start of OLEX) to end of OLEX (week 28)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis for this endpoint

End point values	Idalopirdine 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	1462			
Units: number of TEAEs	2130			

Statistical analyses

No statistical analyses for this end point

Primary: Number of TEAEs in the OLEX-MEM

End point title	Number of TEAEs in the OLEX-MEM[2]
End point description: A TEAE is an adverse event that starts or increased in intensity after the date of Baseline III (start of OLEX-MEM)	
End point type	Primary
End point timeframe: From Baseline III (start of OLEX-MEM) to end of OLEX-MEM (Week 52)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis for this endpoint

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognition

End point title	Change in Cognition

End point description:

Change from Baseline II to Week 28 in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) total score. The ADAS-cog is a 11-item neuropsychological test that assess the severity of cognitive impairment. The items determine the patient's orientation, memory, language, and praxis. Total score of the 11 items range from 0 to 70 (lower score indicates lower cognitive impairment).

End point type	Secondary

End point timeframe:

Baseline II (start of OLEX) to Week 28

End point values	Idalopirdin 60 mg (OLEX): patients from lead-in study 14861A	Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	693	602		
Units: Units on a scale				
arithmetic mean (standard error)	3.01 (± 0.22)	2.67 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression Score

End point title	Clinical Global Impression Score

End point description:

Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) score at Week 28. The ADCS-CGIC is a semi-structured interview to assess clinically relevant changes in patients with AD. The items determine cognition, behavior, social and daily functioning. Severity at baseline is rated on a 7-point scale from 1 (normal, not ill at all) to 7 (among the most extremely ill patients). The clinically relevant change from baseline is rated on a 7-point scale from 1 (marked improvement) to 7 (marked worsening).

End point type	Secondary

End point timeframe:

Week 28

End point values	Idalopirdin 60 mg (OLEX): patients from lead-in study 14861A	Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	693	594		
Units: units on a scale				
arithmetic mean (standard error)	4.58 (± 0.005)	4.61 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Daily Functioning

End point title	Change in Daily Functioning

End point description:

Change from Baseline II to Week 28 in Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL23) total score. The ADCS-ADL23 is a 23-item clinician-rated inventory to assess activities of daily living (conducted with a caregiver or informant). Each item comprises a series of hierarchical sub-questions, ranging from the highest level of independent performance to a complete loss for each activity. Total score of the 23 items ranges from 0 to 78 (higher score indicates lower disability).

End point type	Secondary

End point timeframe:

Baseline II (start of OLEX) to Week 28

End point values	Idalopirdin 60 mg (OLEX): patients from lead-in study 14861A	Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: units on a scale				
arithmetic mean (standard error)	-3.71 (± 0.28)	-3.88 (± 0.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Behavioural Disturbance

End point title	Change in Behavioural Disturbance

End point description:

Change from Baseline II to Week 28 in Neuropsychiatric Inventory (NPI) total score. The NPI is a 12-item structured interview with a caregiver to assess behavioural disturbances. The NPI comprises 10 behavioural and 2 neurovegetative items. Each item consists of a screening question and several sub-questions that are rated no (not present) or yes (present). Each item is rated for frequency (a 4-point scale from 1 [occasionally] to 4 [very frequent]) and severity (a 3-point scale from 1 [mild] to 3 [marked]). The total NPI score is the frequency ratings multiplied by the severity ratings and ranges from 0 to 144 (higher score indicates worse outcome).

End point type	Secondary

End point timeframe:

Baseline II (start of OLEX) to Week 28

End point values	Idalopirdin 60 mg (OLEX): patients from lead-in study 14861A	Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	697	602		
Units: units on a scale				
arithmetic mean (standard error)	1.80 (± 0.35)	1.36 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Aspects of Mental Function

End point title	Change in Cognitive Aspects of Mental Function

End point description:

Change from Baseline II to Week 28 in Mini Mental State Examination (MMSE). The MMSE is an 11-item test to assess the cognitive aspects of mental function. The subtests assess orientation, memory, attention, language, and visual construction. The scores for each item is dichotomous (1 = response is correct, 0 = response is incorrect). Total score of the 11 items ranges from 0 to 30 (higher score indicates lower deficit).

End point type	Secondary

End point timeframe:

Baseline II (start of OLEX) to Week 28

End point values	Idalopirdin 60 mg (OLEX): patients from lead-in study 14861A	Idalopirdin 60 mg (OLEX): patients from lead-in study 14862A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	730	646		
Units: units on a scale				

arithmetic mean (standard error)	-1.28 (± 0.10)	-1.02 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Aspects of Mental Function

End point title	Change in Cognitive Aspects of Mental Function

End point description:

Change from Baseline III to Week 52 in Mini Mental State Examination (MMSE). The MMSE is an 11-item test to assess the cognitive aspects of mental function. The subtests assess orientation, memory, attention, language, and visual construction. The scores for each item is dichotomous (1 = response is correct, 0 = response is incorrect). Total score of the 11 items ranges from 0 to 30 (higher score indicates lower deficit).

End point type	Secondary

End point timeframe:

Baseline III (start of OLEX-MEM) to Week 52

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First dose to follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Idalopirdine 60 mg
Reporting group description: Idalopirdine 60 mg	
Reporting group title	Idalopirdine 60 mg + Memantine
Reporting group description: Idalopirdine 60 mg + Memantine	

Serious adverse events	Idalopirdine 60 mg	Idalopirdine 60 mg + Memantine	
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 1462 (6.22%)	2 / 101 (1.98%)	
number of deaths (all causes)	11	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of cervix uteri			

subjects affected / exposed[1]	1 / 922 (0.11%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Exercise tolerance decreased			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	0 / 1462 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed[2]	1 / 540 (0.19%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast mass			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal haemorrhage			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive symptom			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grief reaction			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical vertebral fracture			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	6 / 1462 (0.41%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Head injury			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia alzheimer's type			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss of consciousness			

subjects affected / exposed	2 / 1462 (0.14%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iris adhesions			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy proliferative			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis e			

subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Otitis media			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			

subjects affected / exposed	3 / 1462 (0.21%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	4 / 1462 (0.27%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 1462 (0.14%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 1462 (0.07%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This Serious Adverse Event is only applicable for female subjects.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This Serious Adverse Event is only applicable for male subjects.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Idalopirdine 60 mg	Idalopirdine 60 mg + Memantine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 1462 (12.45%)	7 / 101 (6.93%)	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	105 / 1462 (7.18%)	6 / 101 (5.94%)	
occurrences (all)	233	11	
Fall			
subjects affected / exposed	80 / 1462 (5.47%)	1 / 101 (0.99%)	
occurrences (all)	93	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2014	Protocol Amendment PA01: The main reason for this amendment is the decision that only patients from lead-in studies 14861A and 14862A will enter into the extension study 14861B. Further, changes of eligibility criteria and clarifications where needed.
16 June 2015	Protocol Amendment CSPA02: for Bulgaria, Canada, Czech Republic, Estonia, Germany, France, Italy, Lithuania, Poland, South Korea, Spain, United Kingdom and United States. AD is a progressive neurodegenerative disease that is characterised by a steady decline in a patient's cognition and function and an increase in behavioural problems. Thus in a complex disease like AD, there is a strong medical need for alternative treatment options which include combining the different symptomatic treatments with diverse pharmacological modes of action. The open-label treatment period with memantine (substudy) will evaluate the safety and tolerability of adding memantine therapy in patients who are already on a stable treatment of idalopirdine and donepezil and for whom memantine treatment is clinically indicated. Concomitant treatment with the three compounds has not been studied in previous or ongoing clinical trials. Furthermore, adjunctive treatment with memantine is likely to be a common treatment option for patients with AD soon after idalopirdine becomes available. Thus the open-label treatment period with memantine (substudy) is designed to inform potential future clinicians and patients of the safety and tolerability profile to expect when idalopirdine, memantine and donepezil are taken concomitantly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: